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Brain Atrophy in Children Undergoing Systemic Chemotherapy for Extracranial Solid Tumors

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It has been shown that intrathecal chemotherapy may cause brain damage, which can be depicted in neuroimaging studies. The aim of this work was to examine possible morphologic alterations in the brain of children with extracranial solid tumors, without CNS complications, treated with systemic chemotherapy. Brain CT images of 69 children with extracranial malignancies were reviewed and the extent of 12 CSF compartments was measured in 49 CT examinations performed during intravenously given chemotherapy and in 20 after therapy completion. Measurements were compared with corresponding normative data. About half of the children undergoing chemotherapy and half of the patients examined after treatment were found to have diffuse brain atrophy. Focal lesions that might be associated with therapy toxicity were not observed. Chemotherapy, even when administered via the systemic route, may cause brain damage, which is observed long after the end of treatment. **Med. Pediatr. Oncol. 28:228–233** © 1997 Wiley-Liss, Inc.

Key words: subarachnoid space; computed tomography; childhood cancer; chemotherapy; therapy toxicity; brain atrophy

INTRODUCTION

Children receiving intrathecal chemotherapy and/or cranial irradiation for acute leukemia or lymphoma have a significant incidence of abnormal findings in neuroimaging examinations related to therapy toxicity [1,2]. Intracranial calcifications, leukoencephalopathy, and more frequently brain atrophy have been observed in children during or after intrathecal treatment [1,3,4]. Furthermore, the severity of brain lesions depicted on CT has been related to the degree of neuropsychologic deficits, mainly concerning the attention, memory, and learning ability of long-term survivors of childhood leukemia [5,6]. Although brain damage caused by intrathecal chemotherapy and cranial irradiation has been extensively investigated, there are only a few reports with limited numbers of patients concerning morphological alterations in the brain of children treated with systemic chemotherapy for extracranial solid tumors [7–9]. These studies have focused on neuroimaging findings in children with neurotoxic symptoms. In the present study, brain CT examinations of children treated for extracranial malignancies without neurologic complications were analysed. In particular, the following were investigated: 1) Were there focal lesions or diffuse brain damage in children receiving intravenously chemotherapeutic agents? 2) Were they observed after systemic chemotherapy completion? 3) What was the radiological pattern of brain lesions? Knowledge of morphologic abnormalities associated with intravenously given antineoplastic drugs may be useful in evaluating side effects of specific therapeutic approaches or in studying sequelae of long-term survivors.

MATERIALS AND METHODS

Sixty-nine children, 41 boys and 28 girls, 18 months to 14 years old, treated for extracranial solid tumors without neurologic complications underwent brain CT in our departments during the last 4 years (January 1991 to January 1995). Eighteen had Wilm's tumor, 17 had neuroblastoma, 11 had soft tissue sarcoma, nine had osteosarcoma, seven had other bone malignancies, four had retinoblastoma, two had germinoma, and one had hepatocarcinoma. Patients were referred for brain CT with various indications, mostly unrelated to their malignancies, but no patient underwent CT just for the purposes of the present study. Forty-nine children were examined by CT during treat-

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TABLE I. Brain Atrophy Distribution in Different Tumor Types

	During treatment (group A, 49 patients)				After treatment (group B, 20 patients)			
Tumor type	Number of Patients	Patients with all CSF spaces enlarged	Patients with several CSF spaces enlarged	Patients with normal CSF spaces	Number of Patients	Patients with all CSF spaces enlarged	Patients with several CSF spaces enlarged	Patients with normal CSF spaces
Wilm's	10	4	1	5	8	3	1	4
Neuroblastoma	13	8	2	3	4	2	1	1
Sarcoma	7	1	1	5	4	2	—	2
Osteosarcoma	7	3	2	2	2	1	1	—
Other bone malign.	6	1	2	3	1	—	1	—
Retinoblastoma	3	2	1	—	1	—	—	1
Germinoma	2	1	—	1	—	—	—	—
Hepatoma	1	—	1	—	—	—	—	—
Sums	49	20	10	19	20	8	4	8

ment with systemic chemotherapy (group A), and 20 were examined after therapy completion (group B). The distribution of tumor types in groups A and B is presented in Table I. In group A, the time interval between the onset of therapy and the CT examination was 1 to 16 months, and in group B, the time elapsed between the completion of therapy and the CT examination was 3 months to 10 years. Children were treated with different combinations of intravenously administered chemotherapeutic agents, and none of them exhibited clinical evidence of neurotoxicity during or after treatment. No patient received intrathecal therapy, cranial irradiation, corticosteroids during treatment, or had a history of cranial trauma or chronic use of corticosteroids. CT examinations had no evidence of space-occupying lesions and no findings of increased intracranial pressure or CNS malformation. The CT scans were reviewed from the CT unit's optical disks, and measurements were obtained after the end of the data collection period.

Examinations were performed on Phillips LX CT scanners with consecutive 5-mm sections in the posterior fossa and skull base and 10-mm sections in the rest of the cranium. Younger children were sedated, when necessary, with 80–100 mg/kg of chlorade hydrate. Using the CT software, the size of the cerebrospinal fluid (CSF) space was estimated by the following measurements: 1) the minimum width of the bodies of the lateral ventricles, 2) the maximum distance between the anterior horns of the lateral ventricles, 3) the bicaudate nuclei distance, the width of the 4) third and 5) fourth ventricles, 6) the anteroposterior and transverse diameters of the basal cistern, which were added, 7) the anteroposterior diameter of the prepontine cistern, the maximum width of the 8) Sylvian and 9) interhemispheric fissures, 10) the maximum width of the peripheral CSF space either at the frontal, temporal, parietal, or occipital regions, and 11) the maximum width of the cortical sulci. The extent of the cerebellar or vermian sulci was assessed qualitatively, since there are no normative data concerning these CSF spaces. To take into account the size and shape of the skull [10], measurements 1–7 were divided by the sum of either the maximal longitudinal and transverse diameters of the skull (measurements 1–4 and 6) or the posterior fossa (measurements 5 and 7). The quotients formed in this manner (CSF indices) were compared with the corresponding normative data (normal range: mean value ± 2 standard deviations). Normative data (mean values, standard deviations, and number of individuals in the aged-matched control groups) were obtained from previous studies [10,11]. The gender was not taken into account, since it has been shown [10] that normal values of CSF indices do not differ between boys and girls. Measurements 8–11 were considered abnormal if they exceeded the corresponding upper normal limits [11] of the Sylvian fissure (3 mm), interhemispheric fissure (4 mm), peripheral CSF space (4 mm), and cortical sulci (2 mm). Data processing and statistical analysis were performed on a computer. The Student t-test was employed to compare the size of the CSF spaces between the children of the present study and the control group and between the CT examinations of groups A and B. Data distribution proximity to normal distribution was assured [12] prior to applying the Student t-test.

RESULTS

The CSF indices employed to measure the extent of the ventricles (bodies of the lateral ventricles, anterior horns, and bicaudate nuclei, distance and width of the third and fourth ventricles) were found to be larger than normal in 47–61% of the cases, and the extraventricular CSF spaces, with the exception of prepontine cistern, were larger in 41–57% of the children of group A examined during treatment (Table II). After the completion of therapy (group B), the ventricles were enlarged in 40–60%, and all the extraventricular CSF spaces—except for the prepontine cistern—were enlarged in 40–55% of the children that had received systemic chemotherapy (Fig. 1).

TABLE II. Measurements of the CSF Compartments of 49 Children Examined During IV Chemotherapy and 20 After Systemic Treatment for Extracranial Malignancies

	During chemotherapy		After treatment	
Measurements	mean ± 2 SD	Abnormal	mean ± 2 SD	Abnormal
LV	0.128 ± 0.035	23 (47%)	0.116 ± 0.046	10 (50%)
AH	0.118 ± 0.038	20 (41%)	0.118 ± 0.041	8 (40%)
BN	0.044 ± 0.014	28 (57%)	0.045 ± 0.011	10 (50%)
TV	0.019 ± 0.007	30 (61%)	0.017 ± 0.009	12 (60%)
FV	0.101 ± 0.022	23 (47%)	0.101 ± 0.031	9 (45%)
BC	0.163 ± 0.041	24 (49%)	0.162 ± 0.058	11 (55%)
PC	0.056 ± 0.021 (mm)	4 (8%)	0.053 ± 0.032 (mm)	3 (15%)
SF	4.2 ± 2.2	28 (57%)	4.6 ± 3.1	11 (55%)
IF	4.6 ± 2.7	23 (47%)	4.4 ± 2.3	9 (45%)
PS	4.3 ± 2.4	26 (53%)	4.7 ± 3.4	11 (55%)
CS	2.2 ± 0.9	24 (49%)	2.6 ± 1.1	9 (45%)
CBs	—	20 (41%)	—	8 (40%)

Indices: LV: Lateral Ventricles Index, AH: Anterior Horns Index, BN: Bicaudate Nuclei Index, TV: Third Ventricle Index, FV: Fourth Ventricle Index, BC: Basal Cistern Index, PC: Prepontine Cistern Index.
Measurements: SF: Sylvian Fissures, IF: Interhemispheric Fissures, CBs: Cerebellar or Vermial Sulci, CS: Cortical Sulci, PS: Maximum width of the CSF space at the frontal, temporal, parietal, or occipital regions.

The extent of the above intra- and extraventricular spaces differed to a statistically significant level ($.001 < P < .05$) from the corresponding measurements of the normal control groups [10,11]. No significant differences ($P > .10$) in the size of the CSF compartments were found between CT examinations performed during and after treatment.

The number of patients with CSF enlargement in each particular type of tumor in groups A and B is presented in Table I; brain atrophy was distributed over all subgroups of children with different types of tumors. Focal low-density lesions or calcifications were not observed in any of our patients. The prepontine cistern was found to be abnormal in two CT examinations performed during treatment and in one performed after treatment.

DISCUSSION

Advances in the treatment of malignant tumors have increased the survival of children with cancer. It is anticipated that by the year 2000 1 in a 1,000 adults will be a survivor of childhood cancer [13]. With the growing number of cured children the late effects of antineoplastic therapies have become more evident [14]. Treatment protocols have to take into account potential side effects of the individual therapeutic intervention in order to minimize complications without loss of efficacy [14]. As a consequence, several studies have attempted to assess health outcomes in survivors of childhood cancer [15]. Neuroimaging methods have been employed in the portrayal of CNS damage after treatment with intrathecal chemotherapy or cranial irradiation [1–4]. Abnormal radiological findings have been described in long-term survivors of pediatric leukemia or lymphoma and have been related to neuropsychologic sequelae [5,6]. However, to our knowledge, potential morphological changes in the brain of children with extracranial solid tumors treated only with intravenously administered chemotherapeutic agents have not been systematically studied. In the present study CT examinations of children treated with systemic chemotherapy for extracranial solid tumors without neurologic involvement were reviewed with emphasis to brain atrophy; the latter has been reported [1,3,4] as the most common radiological finding in children treated with intrathecal chemotherapy or cranial irradiation. Brain atrophy was quantitatively evaluated by measurements of the size of the CSF compartments. In a number of childhood diseases, quantitative assessment of CNS structures can reveal mild morphological abnormalities [16], which are difficult to locate by visual inspection.

According to the results of the present study, about half of the children with extracranial solid tumors were found to have brain atrophy during treatment with systematic chemotherapy. Atrophy was of the diffuse type with equal widening of the ventricular and extraventricular subarachnoid spaces. The brain and the cerebellum were affected similarly. These findings indicate that systemic chemotherapy may cause loss of brain tissue. Despite the blood–brain barrier, low concentrations of the commonly used anticancer drugs or their metabolites have been detected in the CSF, even when administered in conventional doses via the systemic route [17]. It may be, thus, speculated that brain atrophy is the result of chemotherapeutic drugs penetrating the CNS and inducing brain damage.

Neurotoxic symptoms, i.e., dysarthria, nystagmus, ataxia, aphasia, lethargy, hemiparesis, dementia, or coma have been described in children receiving high-dose IV

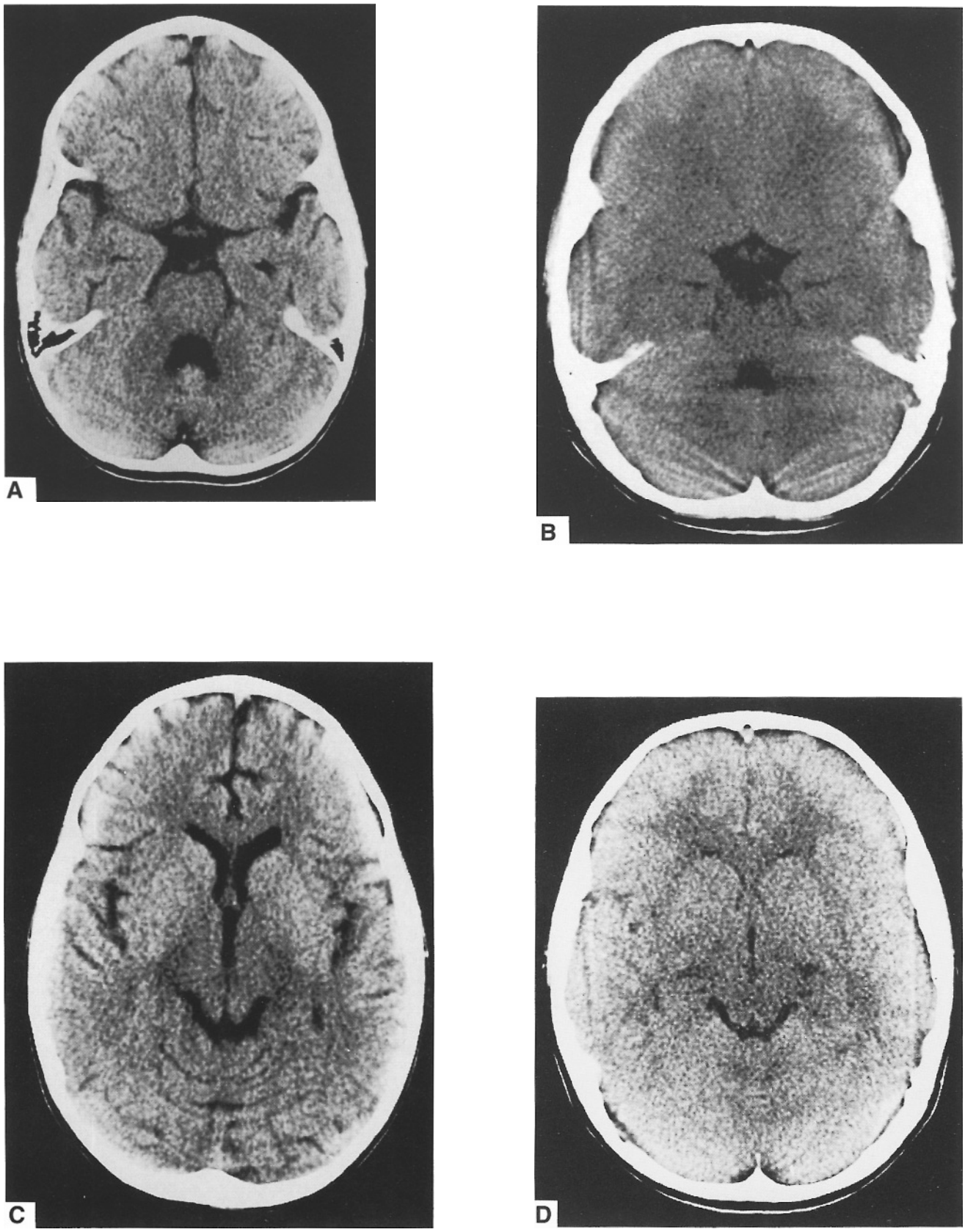

Fig. 1. (legend on following page).

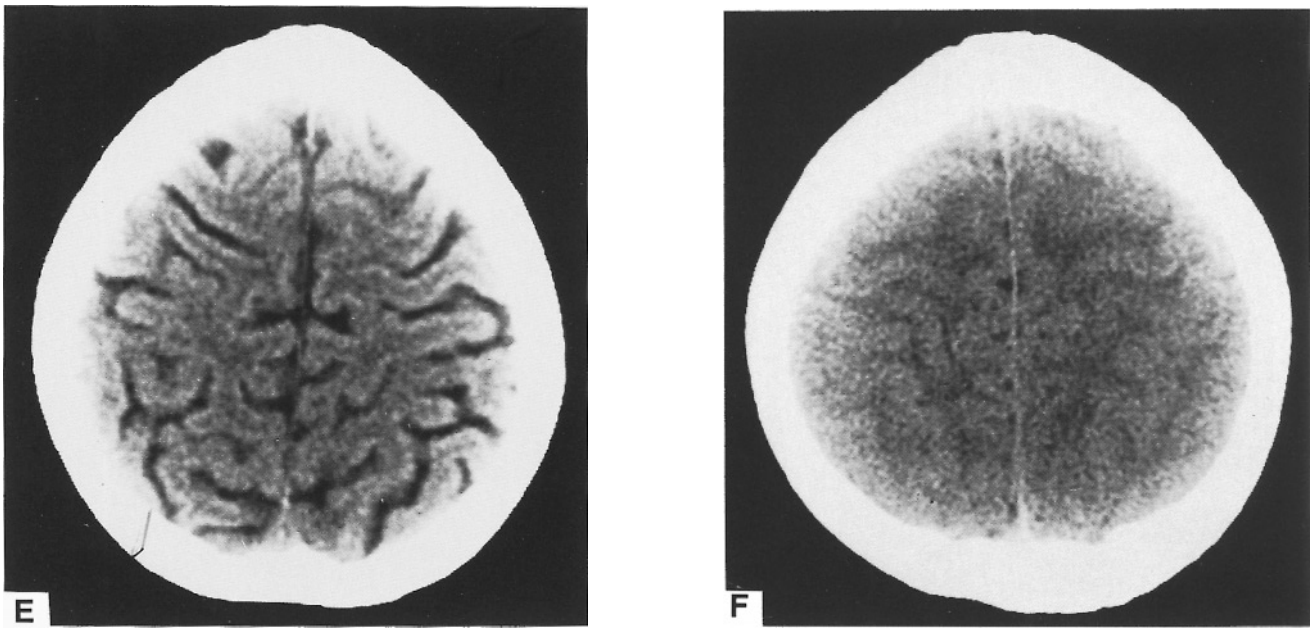

Fig. 1. CT sections through the basal cistern **(A,B),** third ventricle **(C,D),** and cortical sulci **(E,F)** of a 7-year-old boy with Wilm's tumor 1 year after therapy completion (A,C,D), and of a boy of the same age with normal CSF spaces (B,D,F).

methotrexate or cytarabine [13,17]. Abnormal neuroimaging findings have also been reported in children with symptoms of neurologic toxicity: MRI findings of chronic brain edema, white matter necrosis, and deep brain atrophy were observed in four patients treated with high-dose methotrexate [7], cerebellar atrophy was found on CT and MRI in two children receiving high-dose cytarabine [9], and a low absorption area was revealed by CT in a child being treated with intravenously administered high-dose methotrexate [8]. None of the children of the present study exhibited typical symptoms of CNS toxicity, brain metastases, or spinal cord compression, which represent the most common neurologic complications of pediatric solid tumors [18]. Brain atrophy was not associated with obvious clinical symptoms and appeared to represent a subclinical brain damage. It was the only radiological finding in our patients treated with systemic chemotherapy; low-density regions in the white matter or calcifications were not observed in the CT examinations of our patients. These neuroimaging findings have been associated with the toxicity of intrathecally given chemotherapy or irradiation in children with leukemia or lymphoma [1–6].

Widening of the CSF spaces was noted in about half of the children that underwent CT a few months to 10 years after the completion of therapy. Brain atrophy in children that have received systemic chemotherapy has not been described previously. Our finding is in disagreement with the results of a study [19] on brain CT examinations of 18 patients, mostly adolescents, with osteosarcoma who had been treated with high-dose IV methotrexate. No abnormal findings were found in any of the patients of that study; however, examinations were performed on low-resolution old technology CT units, and images were evaluated qualitatively by visual inspection.

The results of the present study were obtained by comparing the width of the CSF spaces of children with extracranial tumors with corresponding normative data [10,11]. It would be preferable if measurements were obtained before, during, and after treatment in the same patient population and if our study population comprised the total number of children treated for extracranial solid tumors in our hospitals instead of the subgroup of patients referred for CT by the clinicians. However, brain CT examinations are not usually included either in the initial or in the follow-up evaluation of children with extracranial solid tumors that do not present neurologic symptoms. The lack of serial CT examinations should not challenge the findings of the present study; brain atrophy observed in our patients can only be attributed to systemic chemotherapy, since there was not an underlying condition (chronic use of corticosteroids or previous cranial trauma) that might have induced brain atrophy.

It is well known that intrathecal chemotherapy and/or cranial irradiation may induce loss of brain tissue in leukemic children [4,6,20]. The incidences of brain atrophy vary significantly, ranging from 8% to 43% among series of brain CT examinations, which have been evaluated visually. However, the frequency of brain atrophy found in the present study is higher than the incidences reported

in leukemic children. This does not imply that systemic chemotherapy causes brain damage in a greater number of cured patients than intrathecal chemotherapy and/or cranial irradiation, but rather that results are not fully comparable owing to the different methods applied in assessing brain atrophy.

In the present study, brain atrophy was observed with similar incidence in children examined during and after treatment. Although this result was obtained from two different groups of patients, it might suggest that brain atrophy induced by systemic chemotherapy persists long after the end of therapy. The clinical significance of these observations and the relationship to neurocognitive function remains uncertain; however, one has to be aware of brain atrophy when interpreting neuroimaging examinations of children with extracranial solid tumors.

In conclusion, the present study has indicated that chemotherapy via the systemic route can induce loss of brain tissue. This subclinical brain damage should be taken into consideration when dealing with long-term survivors of pediatric solid tumors.

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